have significant influence. Recipient with TNFB + 252 G allele-positive was a less significant factor (RR = 1.823, P = 0.063). (3) Relapse was observed more frequently among patients who had not previously developed aGVHD (P = 0.03). Except TNFRII 196 T/T genotype in recipients side was related to lower relapse rate(P = 0.05), no significant association was found between cytokine genes polymorphisms with cGVHD, relapse and overall survival.

Conclusions: These results, which is the first report of TNFA, TNFB and TNFRII polymorphic features of Chinese population with the outcomes of HSCT, suggest an interaction of TNFA-857, TNFB + 252 genotypes on risk of aGVHD.

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RAPID SWITCH TO DONOR-TYPE DOMINANT CHIMERISM AND EARLY LYMPHOCYTE RECOVERY FOLLOWING REDUCED-INTENSITY CORD BLOOD TRANSPLANTATION

Uchida, N.[1], Wake, A.[1], Yamamoto, H.[1], Yoneyama, A.[2], Nishida, A.[1], Shimazu, H.[1], Nakano, N.[1], Ishiwata, K.[1], Tsuji, M.[1], Asano-Mori, Y.[1], Makino, S.[3], Masuoka, K.[4], Taniguchi, S.[1] [1] Toranomon Hospital, Tokyo, Japan; [2] Toranomon Hospital, Tokyo, Japan; [3] Toranomon Hospital, Tokyo, Japan; [4] Misbuku Hospital, Tokyo, Japan

Although immune cells in cord blood (CB) are immature, several lines of evidence suggested that they are potentially active from very early timing post-transplant, such as severe immune reaction observed at around day 9 (Kishi, Transplantation 2005, Barker, BMT Tandem meetings 2009), or the impact of HLA disparity in GVH direction on engraftment failure (Matsuno, Blood 2009). We conducted a retrospective study to investigate the kinetics of donor-recipient chimerism and lymphocyte recovery (LR) during early period after CBT. Data were collected from 109 patients who underwent first CBT using fludarabine (Flu)-containing regimen since June 2007 to Feb. 2009 at Toranomon Hospital. Patients who had non-malignant diseases, died within 30 days, or had disease progression before engraftment or within 30 days post-transplant were excluded, and 47 were subjected to the analysis. 21 out of 26 recipients of unrelated bone marrow (UBM) transplanted during the same period were selected as above and were used as a control. Patients received Flu along with melphalan, busulfan, and total body irradiation in various combinations. Tacrolimus (Tac)+mycophenolate mofetil (n = 42) or Tac alone (n = 5) were used for CB recipients and Tac+methotrexate was for all UBM recipients as GVHD prophylaxis. 1 or 2-antigen mismatched CB units were used at a median 2.56 (1.96-4.31) $\times 10^7$/kg of TNC and 0.87 (0.4-6.32) $\times 10^5$/kg of $CD34^+$ cells. 45 out of 47 CB recipients achieved neutrophil recovery ≥500/μl at a median of 22 (13-43) days, whereas all UBM recipients did at a median of 20 (16-41) days ($P = 0.17$). In CB recipients, 30 patients were assessed donor-recipient chimeric status in 16 days post-transplant, and, remarkably, 28 (93%) achieved complete (>90%) donor-type, while in UBM recipients, 7 were assessed and only 2 (29%) did ($P<.0001$). LR was assessed by defining the first day of 3 consecutive blood test showed lymphocyte (Ly) ≥100/μl as the date of LR. 44 (94%) CB recipients achieved LR at a median of 15 (10-37) days, while all UBM recipients did at a median of 20 (13-29) days ($P = 0.17$). The cumulative incidences of LR achievement up to day 19 were 64 ± 0.5 in CB and 38 ± 1.2 in UBM recipients ($P=.016$). Flow cytometric analysis of Ly at around day 14 (13-17) post-CBT, assessed in 30 patients, showed $CD8^+$ T cell pedominance (50 ± 5% of Ly). In conclusion, the results indicate extremely powerful proliferative potential of CB Ly after transplantation which may surpass that of UBM Ly.

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PREMALIGNANT AND MALIGNANT ORAL CHANGES FOLLOWING ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

Mawardi, H.[1], Elad, S.[2], Correa, M.[3], Stevenson, K.[4], Woo, S.-B.[1,5], Lerman, M.[1,5], Antin, J.[6], Soiffer, R.[6], Treister, N.[1,5] [1] Harvard School of Dental Medicine, Boston, MA; [2] Hebrew University–Hadassah School of Dental Medicine, Jerusalem, Israel; [3] University of Campinas, Sao Paulo, Brazil; [4] Dana-Farber Cancer Institute, Boston, MA; [5] Brigham and Women's Hospital, Boston, MA; [6] Dana-Farber Cancer Institute, Boston, MA

a) Background: Allogeneic hematopoietic cell transplantation (HSCT) is associated with a wide range of complications and late effects, including secondary solid tumors, of which oral carcinoma is one of the most common. The purpose of this study was to describe the clinical characteristics of a large series of patients treated with HSCT that subsequently developed oral premalignant or malignant lesions.

b) Methods: The records of patients who received HSCT and developed oral pre/malignant lesions at 3 centers were reviewed. Descriptive statistics included HSCT course including chronic graft-versus-host disease (cGVHD) and details of oral neoplasm including presentation, diagnosis and management; survival calculations were also performed.

c) Results: Twenty-four patients were identified that developed premalignant (n = 8) or malignant (n = 16) oral mucosal disease at a median time of 3 and 9 years, respectively. Of the 22 that had developed cGVHD, 95% (21/22) presented with oral features. Of those that developed carcinoma, 25% had multifocal involvement. The tongue was the most common site (n = 7; 44%), followed by lower lip and buccal mucosa (n = 2; 12% for both sites). Dysplasia preceded diagnosis of carcinoma in 13% of cases. Localized recurrence occurred in 29% of cases with 5-year freedom from recurrence of 46% ± 16. Five-year overall survival was 75% ± 22 for patients with premalignant changes and 67% ± 16 for patients with carcinoma.

d) Conclusions: Patients undergoing HSCT are at risk of developing new solid cancers, specifically in the mouth. As the majority of patients in this series were previously diagnosed with oral cGVHD, and many cases were multifocal/recurrent, this supports the theory of field cancerization and suggests that these cancers may be more aggressive than in non-HSCT patients. In addition, this highlights the importance of comprehensive oral examination and vigilant follow-up. Further studies examining the biological and molecular processes of tumor development in this high-risk population are needed.

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GENOTYPING OF HUMAN CYTOMEGALOVIRUS (HCMV) IN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS

Dieamant, D.C.[1], Bonon, S.H.A.[1], Murakami, M.M.[1], Costa, S.C.B.[1], Vigorito, A.C.[2] [1] State University of Campinas-UNICAMP, Campinas, São Paulo, Brazil; [2] State University of Campinas-UNICAMP, Campinas, São Paulo, Brazil

Based on sequence variation in the UL55 gene that encodes glycoprotein B (gB), human cytomegalovirus (HCMV) can be classified into four gB genotypes. Previous studies have suggested there could be an association between CMV gB genotype and clinical outcome in patients who underwent an allogeneic hematopoietic stem cell transplant (HSCT).

Objectives: The goal of this study was to determine the distribution of gB genotypes in allogeneic HSCT patients with CMV infection and the effect of gB type on clinical outcome including CMV disease. Study design: DNA was extracted directly from the blood of 41 allogeneic HSCT recipients. Antigen pp65-HCMV and HCMV-DNA was detected by AGM and N-PCR, respectively. The gB genotype of CMV was determined using the polymerase chain reaction to amplify a region of UL55, followed by restriction analysis based on HinfI and RsaI digestion.

Results: At a median time of 32 days after the transplant, 32/41 patients (78%) presented active HCMV infection detected by AGM and/or N-PCR. So far, the distribution of HCMV gB genotypes in 21/32 patients with HCMV active infection was as follow: gB1, 9/21 (42,9%); gB2, 6/21 (28.6%); gB3, 2/21 (9,5%); gB4, 2/21 (9,5%) and two patients (9,5%) had mixed

infection whit gB1+gB3 and gB2 + gB3. HCMV disease developed in 2 patients, characterized for gastrointestinal disease and these two patients had infection with a mixture of HCMV gB genotypes.
Conclusions: in this study the most prevalent genotype in patients with HCMV active infection was gB genotype 1 and moreover, the mixture of HCMV gB genotypes was associate with gastrointestinal disease. However, this study is limited due to the small number of patients, thus making it difficult to draw a firm conclusion regarding the distribution of HCMV genotypes and their possible association with outcome. Nevertheless, these results may be taken as a preliminary report on the prevalence of different HCMV gB genotypes in a Brazilian allogeneic HSCT population with active HCMV infection.

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A PHASE I STUDY OF CLOFARABINE PLUS HIGH DOSE MELPHALAN AS A CONDITIONING REGIMEN FOR ALLOGENEIC TRANSPLANTATION

Kirschbaum, M.H., Stein, A.S., Nakamura, R., Auayporn, N., Popplewell, L., Delioukina, M., Chen, R., Snyder, D., Conrad, J., Frankel, P., Forman, S.J. City of Hope National Cancer Center, Duarte, CA

Background: Reduced intensity regimens for allo transplant successfully replaced the alkylating agent cyclophosphamide with the purine nucleoside antimetabolite, fludarabine, an immunosuppressive with a milder toxicity profile. Clofarabine is a purine nucleoside analogue designed to exploit a double halogen strategy which confers resistance to adenosine deaminase and makes the drug more efficient than fludarabine at inhibiting ribonucleotide reductase and disrupting mitochondrial function, leading to apoptosis.
Aims: To evaluate a clofarabine containing regimen as conditioning for allogeneic stem cell transplant.
Methods: phase I dose escalation: clofarabine (dose level one = 30 mg/m^2, dose level two and three = 40 mg/m2) IV daily days –7 to day –3 infused over 30 minutes IV, plus Melphalan (dose level one and two, 100 mg/m^2, dose level three, 140 mg/m2) administered over 30 minutes IV on day –2. Related or unrelated allogeneic stem cells were infused on day 0. GVHD prophylaxis: initially CSP plus mycophenelate, then tacrolimus plus sirolimus was adopted as per COH standard of care. Patients age ≥ 18 years with AML, ALL, MDS in CR1, CR2 or in relapse (up to 50% marrow blasts), not deemed eligible for standard transplant regimens, or at high risk for relapse, are eligible.
Results: We report on the first 2 dose levels. 10 eligible patients, all with AML, have been treated thus far, 4 Males, 6 Females, with a median age of 62 years (39 – 65). 5 patients were in CR1, 2 patients were in CR2, and 3 patients were transplanted in relapse. Grade 3 non-hematologic toxicities included fatigue, elevation of AST and LFT, diarrhea, and hyponatremia and mucositis (in one patient). No dose limiting toxicities (DLT) were seen in level one. One patient in dose level 2 died prior to engraftment due to hepatic, renal, and infectious toxicities; that dose level has been expanded thus far to seven patients and no further DLT have been seen (one accrued patient was ineligible due to mismatch). Three patients in relapse received an unrelated donor graft, had complete engraftment and achieved remission. Engraftment data is presented in the table below. Mild acute skin graft versus host disease (GvHD) was seen in two patients, with mild gut GvHD responsive to steroids seen in one patient, and mild chronic GvHD in one patient.
Conclusion: The combination of clofarabine and melphalan is an adequate conditioning regimen leading to complete engraftment of allogeneic stem cells.

Dose Level	Patient	Days* to ANC ≥ 0.5x109/L	Days* to PLT ≥ 100	Months Follow-up**	Status
1	1	14	15	20	Remission
1	2	14	13	20	Remission
1	3	24	23	18	Remission
2	4***			1	Expired
2	5	13	13	16	Remission
2	6	17	13	10	Remission
2	7	12	14	8	Remission
2	8	16	14	6	Remission
2	10	12	13	1	Remission
2	11	16	15	1	Remission
	median	14	14	9	

* - From Transplant ** - Days from transplant to relapse/death or last contact *** - Patient expired prior to engraftment.

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DYSGLYCEMIA FOLLOWING GLUCOCORTICOID THERAPY FOR ACUTE GRAFT VS. HOST DISEASE ADVERSELY AFFECTS TRANSPLANTATION OUTCOMES

Pidala, J.[1], Kim, J.[2], Alsina, M.[1], Ayala, E.[1], Field, T.[1], Fernandez, H.[1], Kharfan-Dabaja, M.[1], Ochoa, L.[1], Perez, L.[1], Perkins, J.[1], Tomblyn, M.[1], Anasetti, C.[1] [1]Moffitt Cancer Center, Tampa, FL; [2]Moffitt Cancer Center, Tampa, FL

Disordered glucose metabolism is a common complication of glucocorticoid therapy for acute graft vs. host disease (aGVHD) after allogeneic hematopoietic cell transplantation (HCT). We aimed to examine the independent impact of serum glucose parameters (maximum, minimum, mean, and standard deviation) on outcomes in a series of 173 recipients of HCT who were treated with glucocorticoids for aGVHD. Median onset of aGVHD was 23 days (range 5 – 1112). Patients were treated with primarily 1 mg/kg of glucocorticoids for biopsy-confirmed aGVHD. The median duration of glucocorticoid therapy was 271 days (range 15 – 1632). Glucose values were obtained from glucocorticoid initiation date to death or last follow up, resulting in a total of 13,170 values. The median (range) values for each parameter were: maximum 292 mg/dL (128 – 694), minimum 75 mg/dL (34 – 142), mean 146 mg/dL (86 – 327), and standard deviation 47 mg/dL (12 – 108). Baseline diabetes mellitus predicted significantly greater maximum, mean, and standard deviation. With a median follow up of 18 months, median overall survival (OS) was 16 months (95% CI 11 – 34). On multivariable analysis, maximum glucose significantly predicted OS and non-relapse mortality (NRM). Increased variability also predicted OS and NRM. Those with minimum glucose values of (0 – 60 mg/dL) had increased NRM. Values for minimum glucose demonstrated a non-linear relationship with OS: those with minimum glucose of (0 – 60 mg/dL) as well as those (81 – 150 mg/dL) had significantly worsened OS compared to (61 – 80 mg/dL). Minimum glucose of (81 – 150 mg/dL) was associated with significantly increased risk for relapse. These data demonstrate the adverse effect of dysglycemia in patients treated with glucocorticoids for aGVHD, and argue for stringent glycemic control in this setting. Further efforts to reduce the burden of aGVHD, and its associated treatment with glucocorticoids are paramount.

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ALLOGENEIC HEMATOPOIETIC STEM TRANSPLANTATION DOES NOT ERASE THE IMPACT OF THE NEW PROGNOSIS CLASSIFICATION IN AML AND THE NEGATIVE INFLUENCE OF EVI1 AND FLT3 ITD MUTATIONS

Michallet, M., Sobh, M., Hayette, S., Charlot, C., El Hamri, M., Tedone, N., Nicolini, F.E., Ducastelle, S., Baracco, F., Tigaud, I., Thomas, X. Edouard Herriot Hospital, Lyon, France

We studied 78 patients who underwent an allogeneic HSCT for AML and for whom we had cytogenetics and molecular markers.